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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,752	11/27/2000	Manuel Baca	P1093P1D1	6340

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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,752	BACA ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-47 and 49-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *51 and 52* is/are allowed.

6)☒ Claim(s) *47,49,50 and 53-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 43-44, 46-47, 49-52 have been amended.

Claim 60 has been added.

Claims 43-47, 49-60 are pending and under examination.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

3. The following Office Action contains NEW GROUNDS of rejection.

Rejections Withdrawn

4. The rejection of claims 47, 49-50 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims.

5. The rejection of claims 47, 49-50, 53-56 under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and as evidenced from the specification is withdrawn in view of the new grounds of rejection and amendments to the claims.

6. The rejection of claims 47, 49-50, under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and as evidenced from the specification as applied to claims 43-47, 49-50, 53-56 above, and further in view of Lopez et al (Invest Opthal. And Visual

Science 37:855, 4/96) is withdrawn in view of the amendments tot he claims and the new grounds of rejection.

Response to Arguments

Priority

7. The instant application claims priority to provisional application 60/126,446, filed 4/7/97. Claims 43, recites the limitation of "a Kd value of no more than about 1 X 10-8M" and claims 43 and46 recites the limitation of "in an A673 in vivo tumor model". The limitations have support in the instant application, however, it appears that there is not support for these limitations in the 60/126,446 application. As such the priority date granted to claims 43-47, 49-60 is 8/6/97.

8. The rejection of Claims 43-46, 53-56 under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and as evidenced from the specification is maintained.

The response filed 7/17/03 has been carefully considured but is deemed not to be persuasive. The response states that by simply applying humanization methods of

Adair et al or Yelton et al to the murine antibodies of Ferrara et al one of ordinary skill in the art would not have had a reasonable expectation of success to produce a humanized anti-VEGF antibody variant that had the binding affinity and the inhibition potencies as currently claimed (see page 9 of response). The response then argues that Adair et al showed that even those with increased binding affinity behaved differently in an unpredictable manner in biological activities. The response then addresses the Yelton et al reference by stating that the binding affinity to LeY does not always correlate with binding affinity to tumor cells with LeY bound on their surface (see page 10-11 of response).

In response to these arguments, while Adair et al does teach a general method, the method can be performed on any antibody and all that is required is the screening of many altered antibodies which would not be undue and would have been routine at the time the claimed invention was made. In addition, while the response is directed to an example in Adair et al where binding to cells were reduce even thought the affinity was increased, there is examples in Adair et al, for example the OKT3 humanized antibody which has good binding to cells and had very similar binding in a competition assay (see pages 36 and 51). Thus, there are examples in Adair et al where high affinity and good in vivo binding is taught. In addition, in the example described in the response which showed a lowering in the ability of the antibody to compete with TNF, it would be obvious that a higher concentration would compete better and this is important in view that the claims require a concentration of 5mg/kg which is at a high dose. In response to the Yelton et al argument, there were several mutant antibodies made and while the

M4 was not optimal, the M3 antibody had improved affinity and better binding to H3396 cells (see page 1999 left column last paragraph). With regard to increasing the affinity may not bring a therapeutic advantage, Yelton et al teach that genetic engineering B72.3 resulted in increased affinity and improved radioactivity delivered to the tumor (see page 2002). Thus, it is obvious that better therapeutic advantage can be expected by optimizing the binding of the antibody as taught by Yelton et al.

Thus, both Adair et al and Yelton et al teach that combining mutations can lead to the desired characteristics. This is important because Ferrera et al teach that the antibodies encompassed in Ferrera et al are those that are humanized and have characteristics of good binding affinity and inhibiting angiogenic activity of VEGF at least about 50%-80% and teach the A673 tumor model (see page 8).

9. The rejection of claims 43-46, 53-59 under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and as evidenced from the specification as applied to claims 43-47, 49-50, 53-56 above, and further in view of Lopez et al (Invest Opthal. And Visual Science 37:855, 4/96) is maintained .

The response filed 7/17/03 has been carefully considered but is deemed not to be persuasive. The response did not address this rejection per se. The response addressed the Adair and Yelton reference above and it is assumed the same arguments

would be applied for this rejection and as such the same response above applies. thus the rejection is maintained.

The following are NEW GROUNDS of rejection

Claim Rejections - 35 USC § 112

10. Claims 47, 49-50 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 47 and 49-50 and 60 are indefinite for reciting "FRs are derived" in claim 47. The claims are indefinite for reciting "derived" as the exact meaning of the word is not known. The term “derived” is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the frameworks are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the “derived” framework of the humanized antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term “derived” does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments,

chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 103

11. Claims 43-47, 49-50, 53-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and as evidenced from the specification and Lopez et al (Invest Opthal. And Visual Science 37:855, 4/96) and Bendig et al (U.S. Patent 5,558,864, 11/92).

The claims recite a method of inhibiting VEGF-induced angiogenesis in a subject by administration of an antibody wherein the subject has a tumor wherein the antibody binds no more than 10-9M, and 5mg/kg inhibits at least 50%-80% of tumor growth in a A673 in vivo model, has an ED50 of no more than 50 nM, the antibody comprises CDRs recited in the claims, the antibody is a full length antibody, a IgG, and a Fab and the FR are derived from a consensus sequence and has at least one substitution at position 49, 71, 73, 75, 76 of the heavy chain and at least one substitution at position 46 or 71 in the light chain and wherein the subject has age related macular degeneration and the antibody is administered at a dose of at least about 0.5 mg/kg.

Ferrara et al teach an anti-VEGF antibody (see abstract). Ferrara et al also teach a humanized antibody (see page 8, lines 13-31) and the effect of the antibodies in tumor cell growth and angiogenesis (see page 23-24 and page 4). Ferrara et al also teach methods of inhibiting VEGF-induced angiogenesis in a subject and the subject can have cancer and the antibody was tested in a A673 model (see abstract and Example 2) and the humanized antibody binds with 10-9M affinity (see page 8). Ferrara et al also teach administration at 0.1 to 100 mg/kg (see page 15). Ferrara et al does not teach a specific method for humanization or obtaining the CDR sequence of the antibody or consensus Fr or AMD. These deficiencies are made up for in the teachings of Adair et al, Yelton et al, Lopez et al, and Bendig et al.

Adair et al teach a method of antibody humainzation by CDR grafting and framework modifications and methods of obtaining the amino acid sequences of antibodies from hybridomas and fragments of the antibody such as Fabs (see abstract and entire document) and substitutions at positions in the heavy and light chains, specifically H49, H71, H75, H76, H78 and L46 and L71 (see abstract).

Yelton et al teach an affinity maturation method comprising alterations in the CDRs of the heavy chain (see abstract).

Lopez et al teach VEGF may be important in the progression of ARMD (see page 865) and VEGF is a critical factor in CNVM development (see page 856).

Bendig et al teach humanization of antibodies using a consensus sequence in the FR as well as substitutions at FR positions.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inhibiting VEGF-induced angiogenesis in a subject with AMD by administration of a humanized antibody of Ferrara humanized by the methods of Adair et al, Yelton et al, and Bendig et al in view of Lopez et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method with a humanized anti-VEGF antibody because Adair et al teach "most Mabs are of rodent origin, they are naturally antigenic in humans and thus can give rise to an undesirable immune response termed the HAMA" (see page 2). In addition, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to produce the claimed method because Ferrara et al teach the antibody can be humanized and the tumors from A4.6.1 treated animals were smaller than those tumors in mice treated with a control antibody (see Figure 5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method because Yelton et al teach a method for affinity maturation of an antibody in order to "change the form, affinity, and potentially the specificity of Abs to optimize them for delivering a wide variety of therapeutic agents to tumor cells." (See page 2002 last paragraph). In addition it would have been obvious to humanize the antibody by picking a consensus Fr for the heavy and light chains because Bendig et al teach that effective and specific humanized monoclonal antibodies can be easily obtained by using a consensus sequence)see column 4, lines 13-15) and a consensus

sequence can be synthesized as a whole without problems and there is no dependence on the knowledge or availability of certain individual antibodies (see column 4, lines 38-50).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method because Ferrera et al teach the methods for inhibition of angiogenesis in a subject with many diseases and in view of Lopez which teaches VEGF is involved in angiogenesis in ARMD it would be obvious to inhibit ARMD with a humanized antibody to VEGF.

Moreover, it would have been obvious to humanize the A4.6.1 antibody of Ferrara et al by the methods of Adair et al, Yelton et al, and Bendig et al because Ferrara et al teach human VEGF and in view of Adair and Yelton et al and Bendig et al it would be obvious to humanize the antibody for therapy for inhibiting VEGf-induced angiogenesis.

As evidenced from the specification the A4.6.1 antibody of Ferrara et al has the CDRs as recited in claims 47, 49-50 (see Figure 1A and 1B of the specification).

It is the Examiner's position that the antibody produced by humanizing Ferrara et al's antibody with Adair et al's and Yelton et al's method would produce a humanized antibody that would have the binding and inhibition characteristics claimed in the claimed method. One of ordinary skill in the art would reasonably conclude that Ferrara et al's antibody humanized with Adair et al's and Yelton et al's method also possesses (1) the same binding affinity to the human VEGF, and (2) inhibits angiogenesis and tumor growth of at least about 50% in A673 in vivo tumor model and has an Ed50 of

5nM, therefore, it appears that Ferrara et al's antibody humanized with Adair et al's, Yelton et al's, and Bendig et al's method would produce a humanized antibody that is identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed humanized antibody with the humanized antibody of Ferrara et al's antibody humanized with Adair et al's, Yelton et al's, and Bendig et al's method, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. Claims 51 and 52 are in condition for allowance.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, Ph.D.
PRIMARY EXAMINER